COMMENTARY

Crossroads in Clinical Trials

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INTRODUCTION

If clinical trials are the engine that powers the development of new interventions for neurologic and other diseases, volunteer participants in those trials are the fuel. Yet as attendees at the Advocacy Forum of the 7th Annual Meeting of the American Society for Experimental NeuroTherapeutics (ASENT) heard, the fuel supply is low. "We are facing a national public health crisis. Trust and the incidence of volunteerism in clinical research is declining," said Ken Getz, founder and chairman of the Center for Information and Study on Clinical Research Participation (CISCRP) and a Research Fellow at the Tufts Center for the Study of Drug Development. "Over the past 25 years, as the volume of clinical research has grown dramatically, we have as a community failed to engage the public and prospective volunteers in the process."

A CRISIS FOR CLINICAL TRIALS

Low participation in clinical trials costs dollars as well as lives, Getz added. The National Cancer Institute estimates that only 4% of eligible people actually participate in clinical trials, and professionals who run large clinical trials attribute half of the delays encountered when developing an intervention to the difficulty of enrolling volunteers. A CenterWatch survey of clinical investigation sites found that 90% of clinical trials fail to complete enrollment within the period of time anticipated, resulting in an average delay to completion of at least 6 weeks.

Getz outlined some of the reasons for low participation. First, he said, the public is poorly informed about the clinical trials enterprise. Those conducting trials typically rely on promotional messages delivered through billboards and advertisements as a means of informing the public about the research; however, the information conveyed by these methods is extremely limited. Meanwhile, the news media tend to focus on sensational stories that capture the failure of the research enterprise. Worse, popular media typically portray research volunteers as guinea pigs rather than as individuals who have "made the profound decision to give their gift of participation." Entertainment media such as television and movies carry this one step further, focusing on corruption and greed in the research community, in such popular movies as *The Fugitive*.

Despite these negative portrayals, surveys show that the public continues to believe in the importance of clinical research to advance science, and many individuals claim interest in participating in a clinical trial if asked, said Getz. Yet at the same time, other studies show waning public trust in the ethical conduct of research and the trustworthiness of information coming from the research community.

The data on participation in clinical trials indicate, according to Getz, that the problem is getting worse rather than better, and he maintains that the research community is overlooking issues that would ultimately engage volunteers in the process. Recruitment practices today increasingly rely on sophisticated approaches that employ databases and metrics to target potential volunteers. Another trend has been the increasing practice of recruiting volunteers abroad, especially from Central and Eastern Europe, Latin America, India, and Asia; a practice that could backfire if it is viewed as driven by profit and resource containment.

CONTEXT AT THE HEART OF ENGAGEMENT

The clinical research environment lacks context, continued Getz. The public at large, potential volunteers, and the professionals that conduct trials all need to understand the critical roles they play in the context of the entire research enterprise, which involves millions of people and billions of dollars.

Engaging the public involves outreach and retention. Getz cited one outreach program developed for a closed head injury study. Ambassadors—patients who had been involved in clinical research in the past—were enlisted to talk about their experiences with various community and patient groups. The result of this ambassador program

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was a doubling in the rate of referrals to the study. Getz, however, claimed that even successful programs like this fall short of engaging the public in a long-term way in the process of clinical research because they fail to build national awareness of the importance of this research.

Other steps that are being taken to address waning public trust in the clinical research enterprise include better training of the professionals who conduct clinical studies through university-based clinical research degree programs; increased public disclosure about trials that are underway and the results of those trials; strengthened measures aimed at improving compliance by those conducting trials through Institutional Review Boards (IRBs) and oversight committees; and more attention to protecting the privacy of volunteers. But none of these efforts address the fundamental need to educate the public about clinical research. Education, said Getz, is the key to engaging the population. Participation in clinical trials results in high levels of understanding about the research enterprise and positive attitudes about the experience. But although 89% of volunteers surveyed said they would participate in a trial again, 79% report no follow-up after the study. Few ever learn about the impact their participation had after the trial ends. The potential contribution of these volunteers in outreach efforts for future trials is thus being overlooked.

Lack of follow-up points to another weakness in the system: poor engagement of the physician community. A CenterWatch survey found that although more than three quarters of the public considers medical professionals to be the most trusted source of information, less than 20% learn about clinical trials from their physicians. Less than half of all physicians report referring one of their patients into a clinical trial; and the average referral rate is less than one patient per year. Physicians say it is not concerns about liability or the fear of losing a patient to another practice that prevents them from referring patients for trials; it is more a matter of a not having enough time and not knowing where to find the information they need to give them confidence in making the referral. The referral rate among physicians who have been involved in clinical trials is double that of physicians with no prior experience. In addition, physicians with prior clinical trial experience refer five times the number of patients annually.

Rosalie Lewis, past president of the Dystonia Medical Research Foundation, added that advocacy groups can play an important role in educating the public and facilitating recruitment into trials. Her organization has developed a "Program in the Box," which includes educational information and other awareness materials including lists of potential speakers for community events; and which can be easily distributed to support groups and other interested people around the country. The concept, she said, gets to the grassroots and could be easily adapted by advocacy groups representing other diseases and conditions.

BUILDING TRUST THROUGH INCREASED DISCLOSURE

With patients, physicians, and advocacy groups all demanding increased access to information, Congress has responded by passing more laws mandating increased disclosure; and governmental organizations such as the Food and Drug Administration (FDA) have responded with new regulations and guidelines intended to increase the transparency of clinical trials. Russell Katz, M.D., Director of the Division of Neuropharmacological Drug Products at the FDA, described the evolution of these regulations and statutory requirements, which provide access to the public about the status of clinical research, as well as results of studies after a drug has been approved.

In 1988, Congress passed the Health Omnibus Programs Extension (HOPE) act, which directed the Secretary of Health and Human Services to disseminate information about the treatment of HIV-related disease. The HOPE act set the stage for statutory changes that influence all disease conditions. One of the most important of these was the FDA Modernization Act (FDAMA), passed in 1997. This law directed the Secretary to post clinical trials information about serious and life-threatening illnesses in a publicly accessible database. The information to be posted includes patient eligibility, purpose of the drug, location of trial sites, and information about how to enroll. Results of trials may be posted, but it must come from the published literature rather than unpublished data provided by a sponsor. This is meant to prevent a sponsor from inappropriately "spinning" the results, said Katz. Both federally and nonfederally funded trials are covered by this act. The database, www.clinicaltrials.gov, became operational on 29 February 2000, and the FDA began to educate sponsors about the law and monitor compliance, which so far has been poor. In many therapeutic areas, Katz said, compliance is "somewhere in the single digits."

Meanwhile, in 2004, PhRMA, the Pharmaceutical Research and Manufacturers of America, announced the creation of a central voluntary database presenting results of clinical studies of marketed (not investigational) drugs. The *New England Journal of Medicine* supported this effort by requiring that to get a drug study published, the trial must be registered with a public clinical trial registry. The International Committee of Medical Journal Editors established registry requirements, which include the obligation to publish negative studies.

Two laws address concerns about pediatric trials and marketing of drugs to children. The Best Pharmaceuticals for Children Act (BPCA) provides a voluntary "car-

rot" for sponsors—an additional 6 months of exclusivity—if they include studies of their drug in children. The studies do not have to prove that the drug works in children; the act only requires that they be conducted to obtain additional exclusivity. The act also requires summaries of medical and clinical pharmacology reviews to be posted whether or not the drug is approved for use in children. According to Katz, this is the first time that the FDA has gone on record saying that reviews of applications, even if the applications are not approved, at least for pediatric studies, must be posted. More recently, the Pediatric Research Equity Act (PREA) was passed, which requires sponsors to do pediatric studies, unless they are exempted, for several possible reasons, because the drug would likely be unsafe or ineffective in children.

INFORMING THE PUBLIC THROUGH PRODUCT LABELING

Some, but not all, of the data generated in clinical studies eventually makes its way into the product labeling. Left out of labeling, according to Katz, are data deemed to be uninterpretable or misleading. In addition, some factual information may be left out of the labeling because it could encourage off-label use of the drug. For example, in many cases, if a drug has been approved in adults, pharmacokinetic data generated in children may be excluded from labeling because it would essentially provide dosing information for a drug that may not have been proven safe or effective in children.

Katz said that the recent controversy about the use of antidepressants in children and their association with suicidal behavior has changed the FDA's approach to including pediatric data in product labeling for these drugs. A number of antidepressant studies have been conducted in children and most of these have been negative, meaning that they do not meet statistical rules proving effectiveness. Nonetheless, these studies do not prove that the drugs do not work, and many investigators believe that they do, at least for certain subgroups of children. In the past, such negative results were left out of labeling because the FDA felt that they were uninterpretable and misleading. Now, however, labeling includes information saying that the drug has been tested in pediatric patients but that data have been insufficient to support approval of the drug in children.

Positive results may also be excluded, for example, if the sponsor does not want to include positive studies of the use of a drug in children for fear that it will encourage use and increase their liability risk.

Recent studies about the increased risk of heart disease associated with Cox-2 inhibitors (e.g., Vioxx and Bextra) have resulted in what Katz characterized as a "huge cry" for increased transparency at the FDA. As a result, the agency recently announced new safety initiatives, including the creation of an independent safety board and the earlier inclusion of assessments of safety signals on patient and physician information sheets. This trend toward making information public earlier is, in Katz's view, a "double-edged sword," because the FDA will need to determine when in the course of its evaluation of a potential safety signal it is appropriate to inform the public. Many possible safety signals are ultimately determined to not be related to drug treatment, and informing the public about all potential safety signals would be problematic.

Katz was asked about the FDA's position when a sponsor withdraws a drug or stops clinical trials, even though the FDA might review the data and find the agent to be relatively safe. Katz said the trials may continue in some cases even if a drug has been withdrawn for safety reasons. But if the sponsor ends trials anyway, the FDA is not obligated to state a dissenting opinion about that withdrawal. In response to concerns that patients' voices are left out of the drug development process, the FDA has recently started to hire patients and advocates to serve as consultants at meetings with sponsors of drug applications.

ADVANCING PARKINSON′S THERAPIES (APT): A CASE STUDY IN BUILDING AWARENESS

The final speaker at the Advocacy Forum, Robin Elliott of the Parkinson's Disease Foundation, talked about what one disease community has done to harness the energy of advocacy groups. *Advancing Parkinson's Therapies (APT*) is a collaborative approach designed to accelerate the development of new therapies for Parkinson's disease (PD) by increasing awareness and participation in clinical trials among the Parkinson's community. APT grew out of the recognition that as research on PD moves forward, more clinical trials will be needed, requiring a larger pool of volunteers. By 2006, it is estimated that the number of available trials will out step the availability of volunteers. . .unless something is done to increase awareness among trial participants. The campaign has the support of National Institutes of Health (NIH) Director Dr. Elias Zerhouni, who has noted the demand for volunteers—perhaps as many as 3000—that will be presented by the ongoing neuroprotection trial (NET-PD), sponsored by the National Institute of Neurological Disorders and Stroke. At the same time, groups of patients, such as the Parkinson Pipeline Project (www.pdpipeline.org), have been organizing to get patients more involved in the clinical trials effort.

APT also represented a community-wide understanding that competitiveness among the numerous PD advocacy groups has led to a tremendous waste of resources; and that a coalition effort could replace disarray with

value and strength. The coalition is led by the Parkinson's Disease Foundation in collaboration with American Parkinson Disease Association, the Michael J. Fox Foundation for Parkinson's Research, the National Parkinson Foundation, the Parkinson's Action Network, the Parkinson Alliance, and WE MOVE. The coalition is also advised by National Institute of Neurological Disorders and Stroke, the Parkinson's Study Group, and the Parkinson Pipeline Project. APT has adopted a broad agenda with five main strategies: 1) having PD patients serve as company advisors, tracking company plans and familiarizing themselves with the corporate environment; 2) providing PD patients to serve as advisors on FDA panels and play a formal role in the regulatory process for preapproval of new drugs; 3) encouraging patients with PD to become research partners, supporting others who are considering or participating in trials; 4) adopting the Research Participants Bill of Rights to ensure trust between industry, trial leaders, and patients; and 5) promoting awareness in the PD community about clinical trials to increase the potential pool of volunteers.

The focal point of APT's clinical trials awareness strategy is a comprehensive web site, www.PDtrials.org. In addition to the web site, APT has developed collateral materials, such as a clinical trial guide and a grassroots outreach kit; is providing a toll-free information request line run by an independent third party; and has developed a communication and marketing plan. The awareness campaign is to be collaborative, transparent, and independent of the supporting organizations. It is independently funded by foundations and accepts no corporate support.

To assess the effectiveness of the campaign, APT first set out to establish a baseline. An online and mail survey targeted 17,000 people in the PD community, primarily people with PD or their caregivers. With a return rate of nearly 20%, the online survey found that whereas 94% of respondents were aware of clinical trials in general, only 29% were aware of trials in their geographical area; 79%, however, said they would participate in local trials. Thirty-five percent said they had become aware of clinical trials through a web site; only 19% were told about trials by a physician.

The major goal of the APT campaign is not to increase recruitment into trials, but to raise awareness, said Elliott. Thus, APT has established four major metrics by which they are assessing the success of the campaign during the first year (November 2004 to November 2005). First, they aim to double the number of phone inquiries to PD clinical trial sites in five targeted areas. Second, they aim to increase the number of PD clinical trial phone inquiries to the NIH call center by 75%. The third objective is to reach a position where 25% of the total number of calls to the NIH call center comes from referrals by www.pdtrials.org. Finally, they hope to reach a total number of 1000 unique visitors to the web site per day.

Financial support has so far been "pretty good" for this "bare-bones operation," said Elliott, but he cited a number of challenges that faced the campaign. The first was to create the essential building blocks for the coalition—engendering trust, ensuring confidentiality, and building consensus among seven disparate organizations. Another was obtaining information on the clinical trials themselves—a serious problem when as many as 70% of industry trials are not reported to the FDA. Once trials have been identified, APT depends on collaborations with busy trial coordinators to measure success, all of whom use different tools to gather information. Engaging physicians in the process—a "daunting mountain" not yet tackled—is perhaps the most difficult of the challenges, Elliott said. It is especially difficult because physicians—if they refer patients to trials at all—are likely to refer patients to trials in their home institutions rather than a more appropriate trial at another institution.

TAKING THE NEXT STEP

If the neurotherapeutics community is indeed at a crossroads, as Ken Getz stated, speakers at the Advocacy Forum showed that obstacles on the road have been identified and that first steps have already begun to be taken by the research community, patients, advocates, and the federal government. It will clearly take a partnership of all stakeholders working together, across disease conditions, to generate the level of public support that will be needed to move therapies through the clinical trials process efficiently and expediently.